

**Remarks**

The November 2, 2005 Official Action and references cited therein have been carefully reviewed. In light of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of the application are respectfully requested.

At the outset it is noted that a shortened statutory response period of three (3) months was set forth in the November 2, 2005 Official Action. Therefore, the initial due date for response was February 2, 2006. A petition for a 1 month extension of the response period is presented with this response, which is being filed within the one month extension period.

As another preliminary matter, it is noted that the Examiner has maintained the Restriction Requirement set forth in the July 8, 2005 Official Action and made it final.

At page 5 of the instant Official Action, the Examiner has objected to the specification and claims 1, 11, 20, and 24 for minor typographical errors. Claim 11 has been cancelled and claims 1, 20, and 24 have been amended in accordance with the Examiner's suggestions, thereby rendering the instant objections moot.

Claims 12 and 47 have also been objected to under 37 CFR §1.75(c) for allegedly failing to further limit the subject matter of a previous claim. It is the Examiner's position that "the types of subjects and the "untreated" condition thereof recited in claim 12 are inconsistent with the type of subjects and treatment thereof recited in claim 1, step a)." Applicants respectfully submit that it appears that the Examiner is, in fact, referring to claim 11 and not claim 12. Indeed, the term "untreated" is recited in claim 11, but not claim 12. Applicants have cancelled claim 11, thereby rendering the instant objection moot.

With regard to claim 47, the Examiner alleges that "body fluid" and "urine" samples recited in claim 47 are

inconsistent with the phrase "sample of tissue or cells" recited in claim 1, step b). Applicants have amended claim 1 to recite a "biological sample" instead of "biological sample of tissue or cells," thereby overcoming the instant objection.

The Examiner has also rejected claims 1, 4-6, 9, 11-39, 47, and 48 under 35 U.S.C. §112, second paragraph, for alleged indefiniteness.

Claims 1, 4-6, 9, 11-39, 47, and 48 also stand rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the written description and the enablement requirements.

The Examiner has rejected claims 36-38 under 35 U.S.C. §101 as allegedly lacking patentable utility. While not agreeing with the Examiner's position in this regard, the claims have been rejected, thereby rendering the present rejection moot.

Claims 1, 4, 6, 20, 21, 32-34, 36, 39, and 48 have been rejected under 35 U.S.C. §102(b) as allegedly anticipated by Larsen et al. (WO 98/20124).

Claims 1, 4, 5, 12, 20-23, 26, 32-34, and 48 also stand rejected under 35 U.S.C. §102(a) as allegedly anticipated by or, in the alternative, under 35 U.S.C. §103(a) as allegedly unpatentable over Edvardsson et al. (Electroph. (1999) 20:935-942).

Lastly, claims 1, 4, 12, 13, 20-27, 32-34, and 36-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-4, 14-25, 27, 28, and 30-33 of co-pending Application No. 09/980,422. The Examiner is respectfully requested to hold this double-patenting rejection in abeyance pending the notification of allowable subject matter.

The foregoing objections and rejections constitute all of the grounds set forth in the November 2, 2005 Official Action for refusing the present application.

No new matter has been introduced into this application

by reason of any of the amendments presented herewith.

For the reasons set forth below, Applicants respectfully submit that the objections to claims 1, 11, 12, 20, 24, and 47; the 35 U.S.C. §112, first paragraph rejections of claims 1, 4-6, 9, 11-39, 47, and 48; the 35 U.S.C. §112, second paragraph rejections of claims 1, 4-6, 9, 11-39, 47, and 48; the 35 U.S.C. §102(b) rejection of claims 1, 4, 6, 20, 21, 32-34, 36, 39, and 48; and the 35 U.S.C. §§102(a)/103(a) rejection of claims 1, 4, 5, 12, 20-23, 26, 32-34, and 48, as set forth in the November 2, 2005 Official Action, either lack merit or cannot be maintained in view of the present amendment. These grounds of objection and rejection are, therefore, respectfully traversed.

**The Metes and Bounds of Amended Claims 1, 4-6, 9, 11-39, 47, and 48 Are Clear to One of Skill in the Art**

The Examiner has rejected claims 1, 4-6, 9, 11-39, 47, and 48 under 35 U.S.C. §112, second paragraph for alleged indefiniteness on the following seven grounds.

First, the Examiner contends that claim 1 is generally confusing. Applicants have re-worded claim 1 to address the Examiner's concerns expressed at pages 6 and 7 of the instant Official Action. Specifically, claim 1 has been amended to recite the specific biological samples under study and expressly states that the at least one differentially expressed protein satisfies the three requirements set forth in step (b), i.e., (i) the proteins are differentially expressed between subjects having pancreatic islet or  $\beta$ -cell dysfunction, (e.g., increased or reduced pancreatic islet or  $\beta$ -cell function) (the first biological sample) and normal subjects (the second biological sample); (ii) the proteins are differentially expressed between subjects having reduced or increased pancreatic islet or  $\beta$ -cell function (the first biological sample) and subjects who have been treated by a known treatment or compound which alleviates or improves

pancreatic islet or  $\beta$ -cell function (the third biological sample); and (iii) the proteins are not differentially expressed between normal subjects (the second biological sample) and normal subjects who have been treated by the known treatment or compound (the fourth biological sample). As mentioned, step (a) of amended claim 1 defines the biological samples provided. As the Examiner acknowledges at page 6 of the Official Action, four groups of biological samples are assessed for differential protein expression. Amended step (c) recites a fifth biological sample from a patient treated with an agent or a sample which has been treated with an agent. Step (d) has been amended to recite that the expression level of the at least one differentially expressed protein in the fifth biological sample is compared with that observed in the second or third biological sample. Support for these amendments can be found in claim 1 as previously presented, claims 8-11 as originally filed and at pages 20 to 30 and page 88, line 31 to page 89, line 14 of the instant specification. Applicants respectfully submit that claim 1, as amended, is clear and that the instant rejection is untenable.

Second, the Examiner contends that the term "fa/fa mice lean," recited in claim 12, is unclear. Applicants have deleted the term "lean" from claim 12, thereby overcoming the instant rejection.

Third, it is the Examiner's position that claim 18 is indefinite for recitation of the terms "closely related" and "such as." Applicants have deleted the allegedly indefinite terms from claim 18, thereby rendering the instant rejection moot.

Fourth, the Examiner states that the term "the insulin secretagogue" in claim 31 lacks antecedent basis. Applicants have replaced the term with "the insulin sensitizer drug," which has proper antecedent basis in claim 23.

Fifth, the Examiner contends that the term "protein"

recited in claims 35-37 lacks antecedent basis. Applicants have amended claim 35 to recite "at least one differentially expressed protein."

Sixth, it is the Examiner's position that claims 36 and 37 are confusing for merely reciting a use without any active, positive steps. Applicants have cancelled claims 36 and 37, thereby rendering the instant rejection moot.

Seventh, the Examiner has also rejected claim 38 for allegedly being confusing because it is allegedly unclear how a "high through put screening method" relates to the steps of claim 1. For the reasons set forth below, Applicants have cancelled claim 38, thereby rendering the instant rejection moot.

In light of the above amendment and remarks, the metes and bounds of claims 1, 4-6, 9, 11-39, 47, and 48 are clear and definite to the skilled artisan. Accordingly, Applicants respectfully request that the rejections be withdrawn.

**Amended Claims 1, 4-6, 9, 11-39, 47, and 48 Fully Satisfy the  
Written Description and Enablement Requirements under 35  
U.S.C. §112, First Paragraph**

The Examiner has rejected claims 1, 4-6, 11-39, 47, and 48 for allegedly failing to satisfy the written description requirement of 35 U.S.C. §112, first paragraph for the following five reasons.

First, the Examiner has rejected claim 1 asserting that the recitation of the phrase "treatment with a compound which alleviates or improves pancreatic islet or  $\beta$ -cell dysfunction" introduces new matter. Applicants respectfully disagree with this assertion. As stated hereinabove, support for the amendment to claim 1, which recites the phrase "known treatment or compound which alleviates or improves pancreatic islet or  $\beta$ -cell function," can be found throughout the specification, including, for example, at page 9, lines 4-11;

page 17, lines 29-31; pages 20-30 (see, e.g., page 26, line 35 to page 27, line 3); and page 27, lines 32-35. Accordingly, Applicants respectfully submit that the instant rejection is untenable.

Second, the Examiner has rejected claim 1 asserting that the recitation of the phrase "which undergo a biological change in response to the action of insulin" introduces new matter. Applicants respectfully disagree with this assertion. Support for this phrase can be found throughout the application including, for example, at page 17, lines 17-19. Accordingly, the recitation of the above phrase in claim 1 does not constitute new matter.

Third, it is the Examiner's position that there is no basis for the recitation in step d) of "comparing the results of a) and c)." Specifically, the Examiner alleges there is no disclosure for such a comparison of patterns of differentially expressed proteins from different tissues. Applicants have amended claim 1 to consistently recite that the first, second, third, fourth, and fifth are biological samples such that the discrepancy perceived by the Examiner has been eliminated. Support for this amendment can be found throughout the application, including for example, at page 21, line 24 through page 22, line 7.

Fourth, it is the Examiner's position that the specification fails to disclose any "high through put screening methods," as recited in claim 38. In the sole interest of expediting prosecution of the instant application, Applicants have cancelled claim 38, thereby rendering the instant rejection moot.

Lastly, claims 36-38 have been rejected for allegedly being "reach through" claims. Particularly, the Examiner contends that the "differentially expressed proteins which one would use in the methods of claims 36 and 37 have not been described, except by a vague functional definition, namely that they are 'target proteins.'" In the sole interest of

expediting prosecution of the instant application, Applicants have cancelled claims 36-38. Accordingly, the instant rejection has been rendered moot.

The Examiner has also rejected claims 1, 4-6, 11-39, 47, and 48 for allegedly failing to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph for the following two reasons.

First, it is the Examiner's position that claim 1, as previously presented, called for the "comparison of patterns of differential expression of proteins from different tissues" and that such a comparison is one of "apples against oranges." As stated hereinabove, Applicants have amended claim 1 to encompass analysis of comparable biological samples. Accordingly, amended claim 1 recites the comparison of patterns of differential expression of proteins from the same tissue thereby overcoming the instant rejection.

Second, the Examiner contends that "body fluids or urine samples of claim 47 lack any cells capable" of undergoing "a biological change in response to the action of insulin." Applicants respectfully disagree with the Examiner's position. At page 30, lines 13-16, the instant specification states that "blood and body fluids may be analysed since the differentially expressed proteins in pancreatic islets or  $\beta$ -cells might be released into the circulation." Accordingly, while the agent or known treatment may directly affect pancreatic islets and  $\beta$ -cells, differentially expressed proteins can clearly be monitored in bodily fluids such as blood and urine. Accordingly, Applicants submit that claim 47 is fully enabled by the instant specification.

In light of the above, claims 1, 4-6, 9, 11-39, 47, and 48 fully satisfy the written description and enablement requirements under 35 U.S.C. §112, first paragraph. Withdrawal of the rejections is respectfully requested.

**Claims 1, 4, 6, 20, 21, 32-34, 36, 39, and 48 Are Not  
Anticipated by Larsen et al.**

The Examiner has rejected claims 1, 4, 6, 20, 21, 32-34, 36, 39, and 48 under 35 U.S.C. §102(b) as allegedly anticipated by Larsen et al. (WO 98/20124). The Examiner contends that Larsen et al. disclose a method for identifying proteins which are differentially expressed in diabetic versus normal patients and that such differentially expressed proteins can be used to screen for therapeutic agents. The Examiner concedes that a step by step comparison of claim 1 with the prior art was not performed because of the alleged issues under 35 U.S.C. §112, first and second paragraphs. This rejection is respectfully traversed for the following reasons.

In order to constitute evidence of lack of novelty under 35 U.S.C. §102(b), a prior art reference must identically disclose each and every element of the rejected claim. In re Bond, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990).

Larsen et al. describe a method of identifying diabetes-mediating (DM) proteins by transplanting insulin secreting cells or tissues into host mammals which are at risk of developing diabetes and identifying those proteins which are differentially expressed before the development of diabetes and after the development of diabetes. However, claim 1 as instantly amended recites providing 5 biological samples and the identification of differentially expressed proteins that meet the following three requirements: 1) the proteins are differentially expressed between normal and affected subjects (subjects having reduced or increased pancreatic islet or  $\beta$ -cell dysfunction); 2) the proteins are differentially expressed between affected subjects and affected subjects who have been treated with a known treatment or compound which alleviates or improves pancreatic islet or  $\beta$ -cell function; and 3) the proteins are not differentially expressed between



normal subjects and normal subjects who have been treated with the known treatment or compound. The DM proteins identified by Larsen et al., however, need only to meet ONE requirement, i.e., they are differentially expressed between normal subjects and affected subjects (subjects having diabetes). Furthermore, it is clear that Larsen et al. fails to provide the five biological samples as instantly claimed. Inasmuch the methods taught by Larsen et al. fail to recite each and every element of the instantly claimed methods, Applicants respectfully submit that the instant rejection is untenable. Therefore, the lack of novelty rejection should be withdrawn.

**Claims 1, 4, 5, 12, 20-23, 26, 32-34, and 48 Are Not  
Anticipated by or Obvious over Edvardsson et al.**

Claims 1, 4, 5, 12, 20-23, 26, 32-34, and 48 have been rejected under 35 U.S.C. §102(a) as allegedly anticipated by or, in the alternative, under 35 U.S.C. §103(a) as allegedly unpatentable over Edvardsson et al. (Electroph. (1999) 20:935-942). The Examiner alleges that Edvardsson et al. disclose proteins which are upregulated in ob/ob mice and proposes employing the same method to further study other compounds. Due to the alleged issues under 35 U.S.C. §112, first and second paragraphs, the Examiner concedes that a step by step comparison of claim 1 with the prior art was not performed.

Applicants respectfully disagree with the Examiner's position. As stated hereinabove, claim 1 recites in step a) the providing of four different biological samples which allow for the determination in step b) of differentially expressed proteins based on certain comparisons made between the provided biological samples. Claim 1 also recites a fifth sample treated with the agent of interest. Notably, Edvardsson et al. clearly fail to provide all of the recited samples. As evidenced by Figure 1, Edvardsson et al. study the plasma levels of insulin, triglycerides, and glucose from

lean mice, ob/ob mice, and ob/ob mice treated with WY14,643. Edvardsson et al. clearly fail to provide lean mice treated with WY14,643 for comparison to identify differentially expressed proteins as instantly claimed and fail to provide a fifth biological sample comprising an agent to be analyzed for efficacy in treating a condition characterized by pancreatic islet or  $\beta$ -cell dysfunction.

Inasmuch as a proper rejection under 35 U.S.C. §102 requires the prior art reference to identically disclose each and every element of the rejected claim, Applicants respectfully submit that the instant 35 U.S.C. §102 rejection based on Edvardsson et al. is untenable. Furthermore, it is a well-settled premise in patent law that "silence in a reference is not a proper substitute for adequate disclosure of facts from which a conclusion of obviousness may justifiably follow". In re Burt, 148 U.S.P.Q. 548 (CCPA 1966). Inasmuch as Edvardsson et al. fail to teach and/or suggest each and every element of the instantly claimed invention, Applicants submit that the instant rejection under 35 U.S.C. §103 cannot be reasonably maintained. Accordingly, Applicants respectfully request that the instant rejections of claims 1, 4, 5, 12, 20-23, 26, 32-34, and 48 be withdrawn.

#### CONCLUSION


In view of the amendments presented herewith, and the foregoing remarks, it is respectfully urged that the rejections set forth in the November 2, 2005 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the

Examiner is requested to telephone the undersigned attorney at the phone number give below.

Respectfully submitted,  
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